

## PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

IRVINE, Jonquil, Claire

J. A. Kemp &amp; Co.

14 South Square

Gray's Inn

London WC1R 5LX

ROYAUME-UNI

J. A. KEMP &amp; Co

RECD 2 Nov 1999

Action by JCI/SA

Date of mailing (day/month/year) 18 November 1999 (18.11.99)		IMPORTANT NOTICE	
Applicant's or agent's file reference N.74664A JCI			
International application No. PCT/GB99/01481	International filing date (day/month/year) 11 May 1999 (11.05.99)	Priority date (day/month/year) 11 May 1998 (11.05.98)	
Applicant ISIS INNOVATION LIMITED et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,EP,JP,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

CA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 18 November 1999 (18.11.99) under No. WO 99/58557

**REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)**

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))**

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Genève 20, Switzerland	Authorized officer  J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

EK102712487US

## PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:

J.A. KEMP & CO.  
Attn. IRVINE, Jonquil Claire.  
14 South Square  
Gray's Inn  
London WC1R 5LX  
UNITED KINGDOM

J.A. KEMP &amp; CO.

17 DEC 1999

Action by \_\_\_\_\_

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing  
(day/month/year)

15/12/1999

Applicant's or agent's file reference

N.74664A JCI

**FOR FURTHER ACTION**

See paragraphs 1 and 4 below

International application No.

PCT/GB 99/01481

International filing date  
(day/month/year)

11/05/1999

Applicant

ISIS INNOVATION LIMITED et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Andria Overbeeke-Siepkens

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>N. 74664A JCI</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/01481</b>	International filing date (day/month/year) <b>11/05/1999</b>	(Earliest) Priority Date (day/month/year) <b>11/05/1998</b>
Applicant <b>ISIS INNOVATION LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**DIMERS OF THE HLA-B27 HEAVY CHAIN EXTRACELLULAR DOMAIN AND USES THEREOF**

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 01481

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 11, 16, 17 and 24, as far as in vivo methods are concerned, are directed to a method of treatment/diagnosis practiced on the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION Sheet PCT/ISA/210

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claim 23 relates to a receptor which binds to a dimer or complex as defined in claim 1. Said receptor is defined by reference to a desirable property, namely it binds to a dimer or complex as defined in claim 1. The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the alpha-beta T Cell Receptor, as mentioned in the description on page 24 lines 12 and 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

National Application No

PCT/GB 99/01481

## CLASSIFICATION OF SUBJECT MATTER

1rC 6 C12N15/12 C12N15/62 C12N5/10 C12N1/21 C07K14/705  
 C07K16/28 A61K38/17 A61K39/00 G01N33/50 G01N33/53  
 G01N33/68 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAPPS G ET AL: "In vivo dimeric association of class I MHC heavy chains. Possible relationship to class I MHC heavy chain-beta 2-microglobulin dissociation" J IMMUNOL, vol. 151, no. 1, 1 July 1993 (1993-07-01), pages 159-169, XP002123589 page 166, column 2, line 1 - line 4 ---	1,15
X	CRESSWELL P ET AL: "Dimeric and monomeric forms of HL-A antigens solubilized by detergent" J. IMMUNOL., vol. 114, January 1975 (1975-01), pages 523-525, XP002123805 figure 2 --- -/--	1,15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

30 November 1999

Date of mailing of the international search report

15/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Lonnoy, O

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01481

(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CUVELIER C ET AL: "Expression of T cell receptors alpha beta and gamma delta in the ileal mucosa of patients with Crohn's disease and with spondylarthropathy" CLIN EXP IMMUNOL, vol. 90, no. 2, November 1992 (1992-11), pages 275-279, XP002123806 abstract ---	11,23
P,X	ALLEN R ET AL: "Cutting edge: HLA-B27 can form a novel beta 2-microglobulin-free heavy chain homodimer structure" J. IMMUNOL., vol. 162, no. 9, 1 May 1999 (1999-05-01), pages 5045-5048, XP002123588 the whole document ---	1-10,15, 18,19,21
A	ALLEN R ET AL: "Expression and folding of HLA B27 in vitro" BRITISH JOURNAL OF RHEUMATOLOGY, vol. 37, no. Supp. 1, 1998, page 41 - Abstract 72 XP000856205 Meeting Info: XVth Annual General Meeting of the British Society for Rheumatology, Brighton, UK, April 22-24, 1998 the whole document ---	1-24
A	WHELAN M ET AL: "Chemical reactivity of an HLA-B27 thiol group" EUR J IMMUNOL, vol. 23, no. 12, December 1993 (1993-12), pages 3278-3285, XP002123590 abstract ---	
A	RAGHAVAN M ET AL: "Extended repertoire of permissible peptide ligands for HLA-B2702" PROTEIN SCI, vol. 5, no. 10, 5 October 1996 (1996-10-05), pages 2080-2088, XP002123591 ---	
A	WO 98 12221 A (WILDNER GERHILD) 26 March 1998 (1998-03-26) ---	
A	WO 97 00084 A (WILEY DON C ;BOUVIER MARLENE (US); HARVARD COLLEGE (US)) 3 January 1997 (1997-01-03) ---	
A	WO 92 07070 A (UNIV TEXAS) 30 April 1992 (1992-04-30) -----	

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01481

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9812221	A	26-03-1998	AU 4459797 A EP 0950065 A	14-04-1998 20-10-1999
WO 9700084	A	03-01-1997	NONE	
WO 9207070	A	30-04-1992	US 5489742 A AU 8923191 A	06-02-1996 20-05-1996

EK10271245745

## PCT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

IRVINE Jonquil Claire

J.A. KEMP &amp; CO.

14 South Square

Gray's Inn

London WC1R 5LX

GRANDE BRETAGNE

29 DEC 1999

Action by

JCI SA

NOTIFICATION OF RECEIPT  
OF DEMAND BY COMPETENT INTERNATIONAL  
PRELIMINARY EXAMINING AUTHORITY(PCT Rules 59.3(e) and 61.1(b), first sentence  
and Administrative Instructions, Section 601(a))Date of mailing  
(day/month/year)

21.12.99

Applicant's or agent's file reference

N.74664A JCI

## IMPORTANT NOTIFICATION

International application No.

PCT/GB 99/ 01481

International filing date (day/month/year)

11/05/1999

Priority date (day/month/year)

11/05/1998

Applicant

ISIS INNOVATION LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

09/12/1999

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0, Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer

PITARD J A S

Tel. (+49-89) 2399-2156



EK102712457US

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

**PCT****CHAPTER II****DEMAND**

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>	
Applicant's or agent's file reference N.74664A JCI	
International application No. PCT/GB99/01481	International filing date (day/month/year) 11 MAY 1999
(Earliest) Priority date (day/month/year) 11 MAY 1998	
Title of invention NOVEL MOLECULE AND DIAGNOSTIC METHOD	
<b>Box No. II APPLICANT(S)</b>	
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	
ISIS INNOVATION LIMITED 2 South Parks Road Oxford OX1 3UB United Kingdom	
Telephone No.:	
Facsimile No.:	
Teleprinter No.:	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	
ALLEN, Rachel Louise Department of Pathology Tennis Court Road Cambridge CB2 1QP United Kingdom	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	
BOWNESS, Paul MRC Human Immunology Unit Institute of Molecular Medicine John Radcliffe Hospital Headington Oxford OX3 9DS United Kingdom	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.	

## Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

McMICHAEL, Andrew James  
MRC Human Immunology Unit  
Institute of Molecular Medicine  
John Radcliffe Hospital  
Headington  
Oxford OX3 9DS  
United Kingdom

State (that is, country) of nationality:  
GBState (that is, country) of residence:  
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☒ agent ☐ common representative  
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.  
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.  
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

IRVINE, Jonquil Claire  
 J.A. KEMP & CO.,  
 14 South Square,  
 London, WC1R 5LX,  
 United Kingdom.

Telephone No.:

+44 171 405 3292

Facsimile No.:

+44 171 242 8932

Teleprinter No.:

23676

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:\***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed  
 the description ☐ as originally filed  
☐ as amended under Article 34

the claims ☐ as originally filed  
☐ as amended under Article 19 (together with any accompanying statement)  
☐ as amended under Article 34

the drawings ☐ as originally filed  
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.  
☐ which is the language of a translation furnished for the purposes of international search.  
☐ which is the language of publication of the international application.  
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |  |   |   |        |
|--|---|---|--------|
| 1. translation of international application                              | : |   | sheets |
| 2. amendments under Article 34   | : |   | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : |   | sheets |
| 4. copy (or, where required, translation) of statement under Article 19  | : |   | sheets |
| 5. letter  | : | 1 | sheets |
| 6. other (specify)   | : |   | sheets |

For International Preliminary Examining Authority use only

received                      not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- |  |   |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 4. <input type="checkbox"/> statement explaining lack of signature                                  |
| 2. <input type="checkbox"/> separate signed power of attorney                            | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (specify): Letter   |

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

\_\_\_\_\_  
IRVINE, Jonquil Claire

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

## PCT COOPERATION TREATY

PCT

SA

INFORMATION CONCERNING ELECTED  
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

J. A. KEMP &amp; Co

IRVINE, Jonquil, Claire

J. A. Kemp &amp; Co

14 South Square

Gray's Inn

London WC1R 5LX

ROYAUME-UNI

REC'D - 2 FEB 2000

Date of mailing (day/month/year)

22 January 2000 (22.01.00)

Applicant's or agent's file reference

N.74664A JCI

## IMPORTANT INFORMATION

International application No.

PCT/GB99/01481

International filing date (day/month/year)

11 May 1999 (11.05.99)

Priority date (day/month/year)

11 May 1998 (11.05.98)

Applicant

ISIS INNOVATION LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, CA, JP, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

None

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

S. Cruz

Telephone No. (41-22) 338.83.38

## TENT COOPERATION TREATY

PCT

3A

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

IRVINE, Jonquil, Claire  
J. A. Kemp & Co.  
14 South Square  
Gray's Inn  
London WC1R 5LX  
ROYAUME-UNI

Date of mailing (day/month/year) 02 July 1999 (02.07.99)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference N.74664A JCI	
International application No. PCT/GB99/01481	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 11 May 1999 (11.05.99)	Priority date (day/month/year) 11 May 1998 (11.05.98)
Applicant ISIS INNOVATION LIMITED et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
11 May 1998 (11.05.98)	9810099.3	GB	15 June 1999 (15.06.99)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No. (41-22) 338.83.38



## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

IRVINE, Jonquil, Claire

KEMP &amp; Co

J. A. Kemp &amp; Co.

14 South Square REC'D 12 MAY 2000

Gray's Inn

London WC1R 5LX

ROYAUME-UNI Action by.....

Date of mailing (day/month/year)

28 April 2000 (28.04.00)

Applicant's or agent's file reference

N.74664A JCI

## IMPORTANT NOTIFICATION

International application No.

PCT/GB99/01481

International filing date (day/month/year)

11 May 1999 (11.05.99)

## 1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address

 ISIS INNOVATION LIMITED  
 2 South Parks Road  
 Oxford OX1 3UB  
 United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

Name and Address

 ISIS INNOVATION LIMITED  
 Ewert House  
 Ewert Place  
 Summertown  
 Oxford OX2 7BZ  
 United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned  
☐ the International Searching Authority
 ☒ the elected Offices concerned  
☒ the International Preliminary Examining Authority
 ☐ other:

 The International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland

Authorized officer

Anman QIU



Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

PCT

SA

From the INTERNATIONAL BUREAU

NOTIFICATION OF RECEIPT OF  
RECORD COPY

(PCT Rule 24.2(a))

To:

IRVINE, Jonquil, Claire  
J. A. Kemp & Co.  
14 South Square  
Gray's Inn  
London WC1R 5LX  
ROYAUME-UNI

Date of mailing (day/month/year) 28 June 1999 (28.06.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference N.74664A JCI	International application No. PCT/GB99/01481

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

ISIS INNOVATION LIMITED (for all designated States except US)  
ALLEN, Rachel, Louise et al (for US)

International filing date : 11 May 1999 (11.05.99)  
Priority date(s) claimed : 11 May 1998 (11.05.98)  
Date of receipt of the record copy  
by the International Bureau : 10 June 1999 (10.06.99)  
List of designated Offices :

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE  
National : AU, CA, JP, US

## ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase  
☒ confirmation of precautionary designations  
☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer:  S. Cruz
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

IRVINE, Jonquil, Claire  
J. A. Kemp & Co.  
14 South Square  
Gray's Inn  
London WC1R 5LX  
ROYAUME-UNI

Date of mailing (day/month/year) 28 April 2000 (28.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference N.74664A JCI	
International application No. PCT/GB99/01481	International filing date (day/month/year) 11 May 1999 (11.05.99)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address ISIS INNOVATION LIMITED 2 South Parks Road Oxford OX1 3UB United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input type="checkbox"/> the name	<input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address ISIS INNOVATION LIMITED Ewert House Ewert Place Summertown Oxford OX2 7BZ United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Anman QIU Telephone No.: (41-22) 338.83.38
---	---

PCT  
TENT COOPERATION TREA

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 22 January 2000 (22.01.00)	<b>Applicant's or agent's file reference</b> N.74664A JCI
<b>International application No.</b> PCT/GB99/01481	<b>Priority date (day/month/year)</b> 11 May 1998 (11.05.98)
<b>International filing date (day/month/year)</b> 11 May 1999 (11.05.99)	
<b>Applicant</b> ALLEN, Rachel, Louise et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

09 December 1999 (09.12.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Cruz

Telephone No.: (41-22) 338.83.38

EK102712457US

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

IRVINE Jonquil Claire  
J.A. KEMP & CO.  
14 South Square  
Gray's Inn  
London WC1R 5LX  
GRANDE BRETAGNE

KEMP &amp; Co

REC'D 30 AUG 2000

Action by.....

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year)

25.08.00

Applicant's or agent's file reference  
N.74664A JCI

## IMPORTANT NOTIFICATION

International application No.  
PCT/GB99/01481

International filing date (day/month/year)  
11/05/1999

Priority date (day/month/year)  
11/05/1998

Applicant

ISIS INNOVATION LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

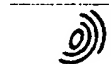
## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Vullo, C

Tel. +49 89 2399-8061



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.74664A JCI	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/01481	International filing date (day/month/year) 11/05/1999	Priority date (day/month/year) 11/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant ISIS INNOVATION LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  09/12/1999	Date of completion of this report  25.08.00
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Vollbach, S  Telephone No. +49 89 2399 8715  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01481

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-26 as originally filed

**Claims, No.:**

1-24 with telefax of 16/05/2000

**Drawings, sheets:**

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 15,20,23,24.

because:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01481

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 23 are so unclear that no meaningful opinion could be formed (*specify*):
- see separate sheet**
- ☒ the claims, or said claims Nos. 15,20,4 are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:
- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:
- see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01481

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	16,17
	No:	Claims	1-5,8,18,19,21,22
Inventive step (IS)	Yes:	Claims	16,17
	No:	Claims	6,7,9-14
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/01481

Re item V:

The present application relates to dimers formed by HLA-B27, diagnostic and therapeutic methods using said dimers.

- D1: CAPPS G ET AL: 'In vivo dimeric association of class I MHC heavy chains. Possible relationship to class I MHC heavy chain-beta 2-microglobulin dissociation' J IMMUNOL, vol. 151, no. 1, 1 July 1993 (1993-07-01), pages 159-169, XP002123589
- D2: WO 92/07070

D1 relates to the finding that a subset of class I MHC molecules including HLA-B27 is capable of association with each other to form disulfide-linked dimers. Homodimer formation is regulated by the availability of  $\beta$ 2-m. Heterodimer formation with  $\beta$ 2m is disclosed to occur normally.

The following considerations with regard to present set of claims apply:

1. Due to the wording "substantially isolated functional dimeric or multimeric analogue..." used in claim 1, the well known complex HLA-B27 with  $\beta$ 2-m is encompassed by said claims. Therefore claim 1 is not new with regard to D1 and the citations made by the applicant in the description of the present application and other documents cited in the search report. The feature of claim 2 is an inherent feature which cannot confer novelty to said claim. The same apply to present claims 3 and 4. Claims 5 relates to the homodimer only which is also disclosed in D1. Therefore present claims 1-5 are no longer new (Article 33(2) PCT). The same apply to present claims 8, 18, 19 and 21.

The transgenic animals as claimed in claims 22 are not new with regard to D2 (and other documents cited in the search report), but said claim additionally is inadmissible under Article 6 PCT for using negative features ("is not") instead of positive and for being indistinguishable from non-transgenic animals.

2. Linking a known complex with biotin which subsequently can bind streptavidin is known to any one skilled in the art. Therefore present claims 6-7 are not considered inventive as required by Article 33(3) PCT.

The methods according to present claims 9-11 and 13-14 are trivial and their

patentability depend on the patentability of the products as such.  
Insofar as claim 12 are concerned an inventive activity cannot be acknowledged, because the preparation of the antibodies directed to a known antigen is routine experimentation only (Article 33(3) PCT).

The method according to present claims 16 and 17 is considered to be new and inventive as required by Articles 33(2) and 33(3) PCT.

3. The gist of the application seems to consist in the finding of a homodimer which is still capable of binding HLA-B27 epitopes. Homodimers are disclosed to possess a modified binding site to which at least the known monoclonal antibodies specific for said binding site do not bind anymore. It is thus concluded in D1 that these homodimers are also incapable of binding their epitopes. It should, however, be noted that in order to render the product i.e. the homodimers novel over D1, a technical distinction between the claimed dimers and those which belong to the state of the art must be apparent. Should there be no such distinction, said function is inherent to the known homodimers (see D1) and thus devoid of novelty. Any technical distinction appears to be essential to the invention and need to be included into the independent claims.

Re item III:

Claim 23 is totally unclear in scope, because the technical nature of the claimed receptor is not indicated neither in the claim nor in the description. Therefore examination with regard to this claim cannot be carried out.

Present claims 15, 20 and 24 are not supported by the application documents and thus completely speculative. Therefore an opinion with regard to novelty and inventive step will not be given for said claims.

Re item IV:

In view of the above novelty objections a common inventive concept between the homodimer and the heterodimer does not exist (Rules 13.1-13.3 PCT).

However, this objection will be prosecuted once the application enters the European regional phase.

Re item VIII:

Claim 15 relates to the use of different compounds in one claims. In order to fulfil the

**INTERNATIONAL PRELIMINARY**

International application No. PCT/GB99/01481

**EXAMINATION REPORT - SEPARATE SHEET**

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requirements of Article 6 PCT, the use of only one of the compounds can be covered by one claim.

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CLAIMS

1. A substantially isolated dimer comprising first and second polypeptides, wherein each of said polypeptides comprises the extracellular domain portions of the HLA-B27 heavy chain and said first and second polypeptides are cross-linked to each other via said extracellular domain portions and are capable of binding an HLA-B27 epitope,  
or a substantially isolated functional dimeric or multimeric analogue thereof which is capable of binding said HLA-B27 epitope and/or competes for binding to a specific receptor for said dimer.
2. A dimer according to claim 1 in which the polypeptides are linked by a disulphide bond between a cysteine residue in the first polypeptide and a cysteine residue in the second polypeptide, said cysteine residues being functionally homologous to Cys 67 of the HLA-B27 heavy chain.
3. A dimer according to claim 1 or claim 2 in which the first and/or second polypeptide comprises residues 1 to 275 of the HLA-B27 heavy chain.
4. A dimer according to any one of the preceding claims in which the first polypeptide and/or the second polypeptide comprise at least the first two N-terminal domains of the HLA-B27 heavy chain.
5. A dimer according to claim 1 in which both polypeptides comprise residues 1 to 275 of HLA-B27 heavy chain cross-linked by a disulphide bond between Cys 67 of each polypeptide.
6. A dimer according to any one of the preceding claims in which the first polypeptide and/or the second polypeptide is linked to biotin.

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7. A complex comprising biotinylated dimers as defined in claim 6 bound to fluorescently-labelled streptavidin in a molar ratio of 4:1.
8. A method of making a dimer as defined in any one of the preceding claims which comprises providing a first polypeptide and a second polypeptide as defined in any one of the preceding claims in conditions in which they cross-link.
9. A method of detecting in a sample the presence of a receptor which binds to a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 which comprises contacting the sample with said dimer or complex.
10. A method according to claim 9 wherein said sample comprises cells from blood or synovial fluid and binding of cells to a complex according to claim 7 is detected by a flow cytometer.
11. A method of determining the onset of, or predisposition to a spondyloarthropathy, comprising measuring the level of, or detecting the presence of, a receptor in the human or animal body which binds to a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8.
12. A monoclonal antibody which binds a dimer as defined in any one of claims 1 to 6, but does not bind to native HLA-B27.
13. A method of determining in a sample the presence of a substance which inhibits the binding of a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 with an antibody as defined in claim 12 comprising:
  - (i) contacting said sample with said dimer or complex in the presence of said antibody; and

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(ii) determining whether binding of said antibody to said dimer or complex is inhibited.

14. A method of determining in a sample the presence of a substance which inhibits the binding of a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 with a receptor as defined in claim 11 comprising:

(i) contacting said sample with said dimer or complex in the presence of said receptor, and

(ii) determining whether binding of said receptor to said dimer or complex is inhibited.

15. A dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8, a monoclonal antibody as defined in claim 12 or a substance determined by a method of claim 13 or 14 for use in a method of treating a spondyloarthropathy or for use as a prophylactic to prevent the onset of a spondylarthropathy.

16. A method of determining the onset of or predisposition to a spondylarthropathy which comprises measuring the level of or detecting the presence of the native homodimer of the heavy chains of HLA-B27 in the human or animal body or in a sample from the human or animal body.

17. A method according to claim 16 in which the homodimer is measured or detected by measuring its binding to an antibody as defined in claim 12.

18. An *ex-vivo* cell which expresses a dimer as defined in any one of claims 1 to 6.

19. A cell according to claim 18 which does not express  $\beta_2$ -microglobulin.

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20. A composition for tolerising a human or animal to the native homodimer of the heavy chains of HLA-B27 which comprises a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8, or a tolerising fragment thereof; or

a cell according to claim 18 or 19;

in association with a pharmaceutically acceptable carrier or diluent.

21. A polynucleotide which encodes a first polypeptide or a second polypeptide as defined in claim 6.

22. A transgenic animal which has been engineered to express a dimer according to any one of claims 1 to 6, wherein said dimer is not a homodimer of the native HLA-B27 heavy chain.

23. A substantially isolated T cell capable of binding a dimer according to any one of claims 1 to 6 or a complex according to claim 7 or a receptor derived therefrom which retains said binding capability.

24. A method of tolerising a human or animal to the native homodimer of the heavy chains of HLA-B27 comprising administering to the human or animal a composition as defined in claim 20.

CLAIMS

1. A substantially isolated dimer comprising first and second cross-linked  
5 polypeptides, wherein said polypeptides comprise the extracellular domain  
portions of the HLA-B27 heavy chain and are capable of binding a HLA-B27  
epitope, or a substantially isolated functional dimeric or multimeric analogue  
thereof which is capable of binding said HLA-B27 epitope and/or competes for  
binding to a specific receptor for said dimer.
- 10 2. A dimer according to claim 1 in which the polypeptides are linked by a disulphide  
bond between a cysteine residue in the first polypeptide and a cysteine residue in  
the second polypeptide, said cysteine residues being functionally homologous to  
Cys 67 of the HLA-B27 heavy chain.
- 15 3. A dimer according to claim 1 or claim 2 in which the first and/or second  
polypeptide comprises residues 1 to 275 of the HLA-B27 heavy chain.
- 20 4. A dimer according to any one of the preceding claims in which the first  
polypeptide and/or second polypeptide comprise at least the first two N-terminal  
domains of the HLA-B27 heavy chain.
- 25 5. A dimer according to claim 1 in which both polypeptides comprise residues 1 to  
275 of HLA-B27 heavy chain cross-linked by a disulphide bond between Cys 67  
of each polypeptide.
6. A dimer according to any one of the preceding claims in which the first  
polypeptide and/or the second polypeptide is linked to biotin.
- 30 7. A complex comprising biotinylated dimers as defined in claim 6 bound to  
fluorescently-labelled streptavidin in a molar ratio of 4:1.

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8. A method of making a dimer as defined in any one of the preceding claims which comprises providing a first polypeptide and a second polypeptide as defined in any one of the preceding claims in conditions in which they cross-link.
- 5 9. A method of detecting in a sample the presence of a receptor which binds to a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 which comprises contacting the sample with said dimer or complex.
- 10 10. A method according to claim 9 wherein said sample comprises cells from blood or synovial fluid and binding of cells to a complex according to claim 7 is detected by a flow cytometer.
11. A method of determining the onset of, or predisposition to a spondyloarthropathy,  
15 comprising measuring the level of, or detecting the presence of, a receptor in the human or animal body which binds to a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8.
12. A monoclonal antibody which binds a dimer as defined in any one of claims 1 to  
20 6, but does not bind to native HLA-B27.
13. A method of determining in a sample the presence of a substance which inhibits the binding of a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 with an antibody as defined in claim 12  
25 comprising:  
(i) contacting said sample with said dimer or complex in the presence of said antibody; and  
(ii) determining whether binding of said antibody to said dimer or complex is inhibited.  
30
14. A method of determining in a sample the presence of a substance which inhibits

-29-

the binding of a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8 with a receptor as defined in claim 11 comprising:

- 5 (i) contacting said sample with said dimer or complex in the presence of said receptor; and
- (ii) determining whether binding of said receptor to said dimer or complex is inhibited.

10 15. A dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8, a monoclonal antibody as defined in claim 12 or a substance determined by a method of claim 13 or 14 for use in a method of treating a spondyloarthropathy or for use as a prophylactic to prevent the onset of a spondylarthropathy.

15 16. A method of determining the onset of or predisposition to a spondylarthropathy which comprises measuring the level of or detecting the presence of the native homodimer of the heavy chains of HLA-B27 in the human or animal body or in a sample from the human or animal body.

20 17. A method according to claim 16 in which the homodimer is measured or detected by measuring its binding to an antibody as defined in claim 12.

18. An *ex-vivo* cell which expresses a dimer as defined in any one of claims 1 to 6.

25 19. A cell according to claim 18 which does not express  $\beta_2$ -microglobulin.

20. A composition for tolerising a human or animal to the native homodimer of the heavy chains of HLA-B27 which comprises a dimer or complex as defined in any one of claims 1 to 7 or made by a method as defined in claim 8, or a tolerising fragment thereof; or

30 a cell according to claim 18 or 19;

-30-

in association with a pharmaceutically acceptable carrier or diluent.

21. A polynucleotide which encodes a first polypeptide or a second polypeptide as defined in claim 6.
- 5
22. A transgenic animal which has been engineered to express a dimer according to any one of claims 1 to 6, wherein said dimer is not a homodimer of the native HLA-B27 heavy chain.
- 10
23. A substantially isolated receptor as defined in claim 11 or substantially isolated cells bearing such a receptor.
24. A method of tolerising a human or animal to the native homodimer of the heavy chains of HLA-B27 comprising administering to the human or animal a
- 15
- composition as defined in claim 20.

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PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) N.74664A JCI

## Box No. I TITLE OF INVENTION

NOVEL MOLECULE AND DIAGNOSTIC METHOD

## Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ISIS INNOVATION LIMITED  
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☐ This person is also inventor.

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Facsimile No.

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State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  
for the purposes of:

☐ all designated  
States

☒ all designated States except  
the United States of America

☐ the United States  
of America only

☐ the States indicated in  
the Supplemental Box

## Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ALLEN, Rachel Louise,  
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Cambridge,  
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United Kingdom.

This person is:

☐ applicant only

☒ applicant and inventor.

☐ inventor only (If this check-box  
is marked, do not fill in below.)

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  
for the purposes of:

☐ all designated  
States

☐ all designated States except  
the United States of America

☒ the United States  
of America only

☐ the States indicated in  
the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

## Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

IRVINE, Jonquil Claire  
J.A. KEMP & CO.,  
14 South Square,  
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23676

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Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS			
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>			
<p>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</p> <p>BOWNESS, Paul, MRC Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DS, United Kingdom.</p>		<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>	
<p>State (that is, country) of nationality: GB</p>		<p>State (that is, country) of residence: GB</p>	
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>			
<p>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</p> <p>McMICHAEL, Andrew James, MRC Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DS, United Kingdom.</p>		<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>	
<p>State (that is, country) of nationality: GB</p>		<p>State (that is, country) of residence: GB</p>	
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>			
<p>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</p>		<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>	
<p>State (that is, country) of nationality:</p>		<p>State (that is, country) of residence:</p>	
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>			
<p>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</p>		<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>	
<p>State (that is, country) of nationality:</p>		<p>State (that is, country) of residence:</p>	
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>			
<p><input type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.</p>			

## Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

## Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

## National Patent (if other kind of protection or treatment desired, specify on dotted line):

- |   |   |
|---|---|
| <input type="checkbox"/> AL Albania                               | <input type="checkbox"/> LS Lesotho                                   |
| <input type="checkbox"/> AM Armenia                               | <input type="checkbox"/> LT Lithuania                                 |
| <input type="checkbox"/> AT Austria                               | <input type="checkbox"/> LU Luxembourg                                |
| <input checked="" type="checkbox"/> AU Australia                  | <input type="checkbox"/> LV Latvia                                    |
| <input type="checkbox"/> AZ Azerbaijan                            | <input type="checkbox"/> MD Republic of Moldova                       |
| <input type="checkbox"/> BA Bosnia and Herzegovina                | <input type="checkbox"/> MG Madagascar                                |
| <input type="checkbox"/> BB Barbados                              | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input type="checkbox"/> BG Bulgaria                              |   |
| <input type="checkbox"/> BR Brazil                                | <input type="checkbox"/> MN Mongolia                                  |
| <input type="checkbox"/> BY Belarus                               | <input type="checkbox"/> MW Malawi                                    |
| <input checked="" type="checkbox"/> CA Canada                     | <input type="checkbox"/> MX Mexico                                    |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein  | <input type="checkbox"/> NO Norway                                    |
| <input type="checkbox"/> CN China                                 | <input type="checkbox"/> NZ New Zealand                               |
| <input type="checkbox"/> CU Cuba                                  | <input type="checkbox"/> PL Poland                                    |
| <input type="checkbox"/> CZ Czech Republic                        | <input type="checkbox"/> PT Portugal                                  |
| <input type="checkbox"/> DE Germany                               | <input type="checkbox"/> RO Romania                                   |
| <input type="checkbox"/> DK Denmark                               | <input type="checkbox"/> RU Russian Federation                        |
| <input type="checkbox"/> EE Estonia                               | <input type="checkbox"/> SD Sudan                                     |
| <input type="checkbox"/> ES Spain                                 | <input type="checkbox"/> SE Sweden                                    |
| <input type="checkbox"/> FI Finland                               | <input type="checkbox"/> SG Singapore                                 |
| <input type="checkbox"/> GB United Kingdom                        | <input type="checkbox"/> SI Slovenia                                  |
| <input type="checkbox"/> GD Grenada                               | <input type="checkbox"/> SK Slovakia                                  |
| <input type="checkbox"/> GE Georgia                               | <input type="checkbox"/> SL Sierra Leone                              |
| <input type="checkbox"/> GH Ghana                                 | <input type="checkbox"/> TJ Tajikistan                                |
| <input type="checkbox"/> GM Gambia                                | <input type="checkbox"/> TM Turkmenistan                              |
| <input type="checkbox"/> HR Croatia                               | <input type="checkbox"/> TR Turkey                                    |
| <input type="checkbox"/> HU Hungary                               | <input type="checkbox"/> TT Trinidad and Tobago                       |
| <input type="checkbox"/> ID Indonesia                             | <input type="checkbox"/> UA Ukraine                                   |
| <input type="checkbox"/> IL Israel                                | <input type="checkbox"/> UG Uganda                                    |
| <input type="checkbox"/> IN India                                 | <input checked="" type="checkbox"/> US United States of America       |
| <input type="checkbox"/> IS Iceland                               |   |
| <input checked="" type="checkbox"/> JP Japan                      | <input type="checkbox"/> UZ Uzbekistan                                |
| <input type="checkbox"/> KE Kenya                                 | <input type="checkbox"/> VN Viet Nam                                  |
| <input type="checkbox"/> KG Kyrgyzstan                            | <input type="checkbox"/> YU Yugoslavia                                |
| <input type="checkbox"/> KP Democratic People's Republic of Korea | <input type="checkbox"/> ZW Zimbabwe                                  |
|   |   |
| <input type="checkbox"/> KR Republic of Korea                     |   |
| <input type="checkbox"/> KZ Kazakhstan                            |   |
| <input type="checkbox"/> LC Saint Lucia                           |   |
| <input type="checkbox"/> LK Sri Lanka                             |   |
| <input type="checkbox"/> LR Liberia                               |   |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ AE United Arab Emirates
- ☐ ZA South Africa
- ☐

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claim indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: * regional Office	international application: receiving Office
item (1) 11/05/98 (11 May 1998)	9810099.3	United Kingdom		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1) ONE

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(iii)). See Supplemental Box.

### Box No. VII INTERNATIONAL SEARCHING AUTHORITY

**Choice of International Searching Authority (ISA)**  
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen: the two-letter code may be used):

ISA / EPO

**Request to use results of earlier search; reference to that search** (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

### Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 4

description (excluding sequence listing part) : 26

claims : 4

abstract : 1

drawings : 13

sequence listing part of description : -

Total number of sheets : 48

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): PF 23/77

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

### Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

IRVINE, Jonquil Claire

For receiving Office use only		2. Drawings:  <input type="checkbox"/> received:  <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

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